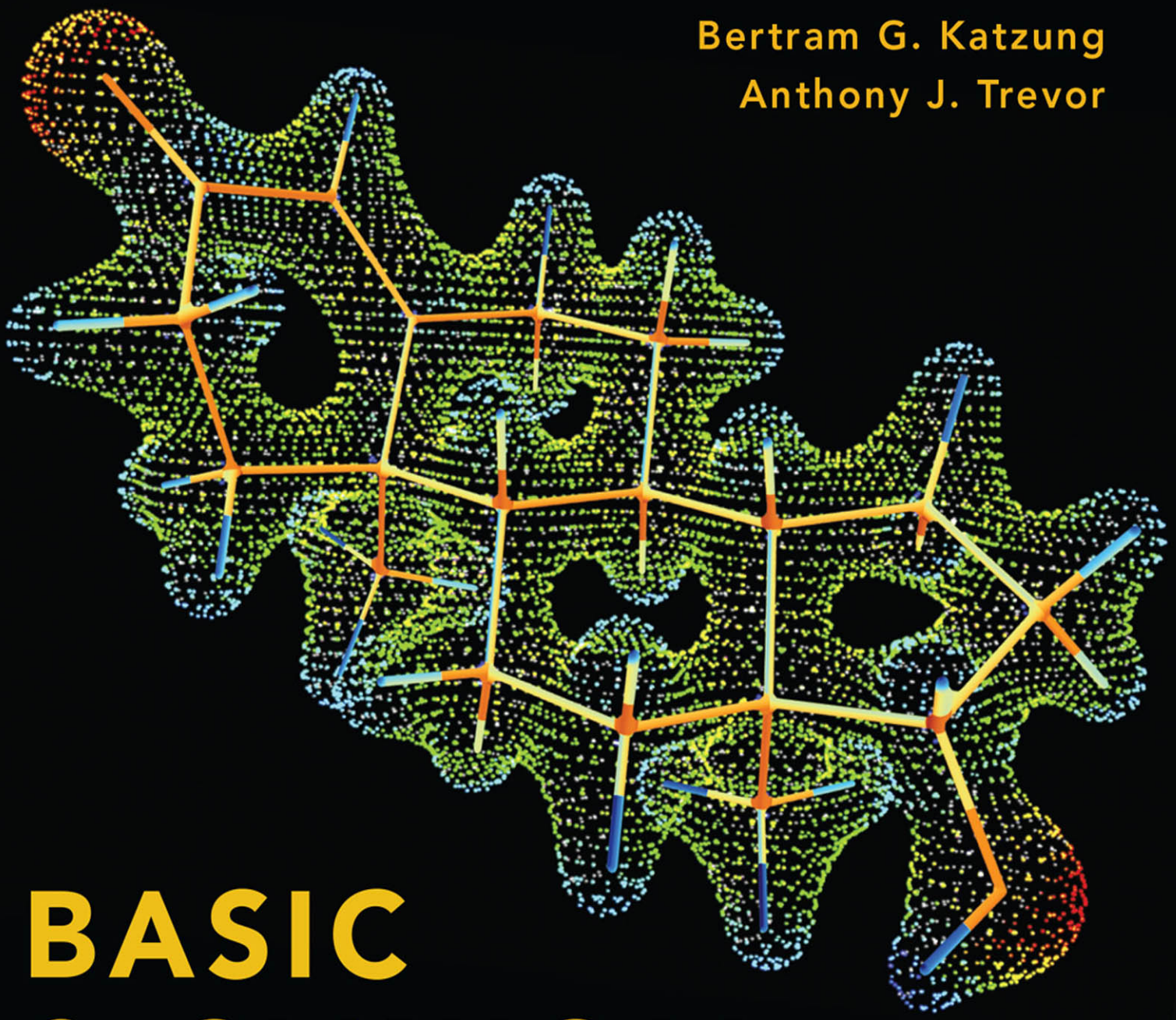
Bertram G. Katzung
Anthony J. Trevor



BASIC & CLINICAL PHARMACOLOGY

13th Edition

McGraw Hill Education
LANGE®

SCHEDULE OF CONTROLLED DRUGS[1]

SCHEDULE I

(All nonresearch use illegal under federal law.)

Flunitrazepam (Rohypnol)

Narcotics:

Heroin and many nonmarketed synthetic narcotics

Hallucinogens:

LSD

MDA, STP, DMT, DET, mescaline, peyote, bufotenine, ibogaine, psilocybin, phencyclidine (PCP; veterinary drug only)

Marijuana

Methaqualone

SCHEDULE II

(No telephone prescriptions, no refills.)[2]

Opioids:

Opium

Opium alkaloids and derived phenanthrene alkaloids: codeine, morphine (Avinza, Kadian, MSContin, Roxanol), hydrocodone and hydrocodone combinations (Zohydro ER, Hycodan, Vicodin, Lortab), hydromorphone (Dilaudid), oxymorphone (Exalgo), oxycodone (dihydroxycodeinone, a component of Oxycontin, Percodan, Percocet, Roxicodone, Tylox)

Designated synthetic drugs: meperidine (Demerol), methadone, levorphanol (Levo-Dromoran), fentanyl (Duragesic, Actiq, Fentora), alfentanil (Alfenta), sufentanil (Sufenta), remifentanil (Ultiva), tapentadol (Nycynta)

Stimulants:

Coca leaves and cocaine

Amphetamines: Amphetamine complex (Biphetamine), Amphetamine salts (Adderall), Dextroamphetamine (Dexedrine, Procentra), Lisdexamfetamine (Vyvanse), Methamphetamine (Desoxyn), Methylphenidate (Ritalin, Concerta, Methylin, Daytrana, Medadate), Above in mixtures with other controlled or uncontrolled drugs

Cannabinoids:

Nabilone (Cesamet)

Depressants:

Amobarbital (Amytal)

Pentobarbital (Nembutal)

Secobarbital (Seconal)

SCHEDULE III

(Prescription must be rewritten after 6 months or five refills.)

Opioids:

Buprenorphine (Buprenex, Subutex)

Mixture of above Buprenorphine and Naloxone (Suboxone)

The following opioids in combination with one or more active non-opioid ingredients, provided the amount does not exceed that shown:

Codeine and dihydrocodeine: not to exceed 1800 mg/dL or 90 mg/tablet or other dosage unit

Opium: 500 mg/dL or 25 mg/5 mL or other dosage unit (paregoric)

Stimulants:

Benzphetamine (Didrex)

Phendimetrazine (Bontril)

Depressants:

Schedule II barbiturates in mixtures with noncontrolled drugs or in suppository dosage form

Barbiturates (butabarbital [Butisol], butalbital [Fiorinal])

Ketamine (Ketalar)

Cannabinoids:

Dronabinol (Marinol)

Anabolic Steroids: Fluoxymesterone (Androxy), Methyltestosterone (Android, Testred, Methitest), Nandrolone decanoate (Deca-Durabolin) Non US, Nandrolone phenpropionate (Durabolin) Non US, Oxandrolone (Oxandrin), Oxymetholone (Androl-50), Stanozolol (Winstrol), Testolactone (Teslac), Testosterone and its esters

SCHEDULE IV

(Prescription must be rewritten after 6 months or five refills; differs from Schedule III in penalties for illegal possession.)

Opioids:

Butorphanol (Stadol)

Difenoxin 1 mg + atropine 25 mcg (Motofen)

Pentazocine (Talwin)

Stimulants:

Armodafinil (Nuvigil)

Diethylpropion (Tenuate) not in US

Modafinil (Provigil)

Phentermine (Ionamin, Adipex-P)

Depressants:

Benzodiazepines: Alprazolam (Xanax), Chlordiazepoxide (Librium), Clonazepam (Klonopin), Clorazepate (Tranxene), Diazepam (Valium), Estazolam (ProSom), Flurazepam (Dalmane), Halazepam (Paxipam), Lorazepam (Ativan), Midazolam (Versed), Oxazepam (Serax), Prazepam (Centrax), Quazepam (Doral), Temazepam (Restoril) Triazolam (Halcion)

Chloral hydrate (Somnote)

Eszopiclone (Lunesta)

Lacosamide (Vimpat)

Meprobamate (Equanil, Miltown, etc)

Methobarbital (Mebaral)

Methohexital (Brevital)

Paraldehyde

Phenobarbital

Zaleplon (Sonata)

Zolpidem (Ambien)

SCHEDULE V

(As any other nonopioid prescription drug)

Codeine: 200 mg/100 mL

Difenoxin preparations: 0.5 mg + 25 mcg atropine

Dihydrocodeine preparations: 10 mg/100 mL

Diphenoxylate (not more than 2.5 mg and not less than 0.025 mg of atropine per dosage unit, as in Lomotil)

Ethylmorphine preparations: 100 mg/100 mL

Opium preparations: 100 mg/100 mL

Pregabalin (Lyrica)

Pyrovalerone (Centroton, Thymergix)

[1]See http://*www.usdoj.gov/dea/pubs/scheduling.html* for additional details.

[2]Emergency prescriptions may be telephoned if followed within 7 days by a valid written prescription annotated to indicate that it was previously placed by telephone.

a LANGE medical book

Basic & Clinical Pharmacology

Thirteenth Edition

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Preface

The thirteenth edition of *Basic & Clinical Pharmacology* continues the important changes inaugurated in the eleventh edition, with extensive use of full-color illustrations and expanded coverage of transporters, pharmacogenomics, and new drugs. Case studies accompany most chapters and answers to questions posed in the case studies appear at the end of each chapter. As in prior editions, the book is designed to provide a comprehensive, authoritative, and readable pharmacology textbook for students in the health sciences. Frequent revision is necessary to keep pace with the rapid changes in pharmacology and therapeutics; the 2–3 year revision cycle of the printed text is among the shortest in the field and the availability of an online version provides even greater currency. The book also offers special features that make it a useful reference for house officers and practicing clinicians.

Information is organized according to the sequence used in many pharmacology courses and in integrated curricula: basic principles; autonomic drugs; cardiovascular-renal drugs; drugs with important actions on smooth muscle; central nervous system drugs; drugs used to treat inflammation, gout, and diseases of the blood; endocrine drugs; chemotherapeutic drugs; toxicology; and special topics. This sequence builds new information on a foundation of information already assimilated. For example, early presentation of autonomic nervous system pharmacology allows students to integrate the physiology and neuroscience they have learned elsewhere with the pharmacology they are learning and prepares them to understand the autonomic effects of other drugs. This is especially important for the cardiovascular and central nervous system drug groups. However, chapters can be used equally well in courses and curricula that present these topics in a different sequence.

Within each chapter, emphasis is placed on discussion of drug groups and prototypes rather than offering repetitive detail about individual drugs. Selection of the subject matter and the order of its presentation are based on the accumulated experience of teaching this material to thousands of medical, pharmacy, dental, podiatry, nursing, and other health science students.

Major features that make this book particularly useful in integrated curricula include sections that specifically address the clinical choice and use of drugs in patients and the monitoring of their effects—in other words, *clinical pharmacology* is an integral part of this text. Lists of the trade and generic names of commercial preparations available are provided at the end of each chapter for easy reference by the house officer or practitioner writing a chart order or prescription.

Significant revisions in this edition include:

- Addition of a chapter on pharmacogenomics, an area of increasing importance in all aspects of pharmacology. The drug development and regulation material previously covered in Chapter 5 has been incorporated into Chapter 1.
- A generic name–trade name table appears at the conclusion of most chapters, providing a rapid reference for these names.
- Many revised illustrations in full color provide significantly more information about drug mechanisms and effects and help to clarify important concepts.
- Major revisions of the chapters on sympathomimetic, diuretic, antipsychotic, antidepressant, antidiabetic, anti-inflammatory, and antiviral drugs, prostaglandins, nitric oxide, hypothalamic and pituitary hormones, central nervous system neurotransmitters, immunopharmacology, and toxicology.
- Continued expansion of the coverage of general concepts relating to newly discovered receptors, receptor mechanisms, and drug transporters.
- Descriptions of important new drugs released through August 2014.

An important related educational resource is *Katzung & Trevor's Pharmacology: Examination & Board Review*, tenth edition (Trevor AJ, Katzung BG, & Masters SB: McGraw-Hill, 2013). This book provides a succinct review of pharmacology with approximately one thousand sample examination questions and answers. It is especially helpful to students preparing for board-type examinations. A more highly condensed source of information suitable for review purposes is *USMLE Road Map: Pharmacology*, second edition (Katzung BG, Trevor AJ: McGraw-Hill, 2006).

This edition marks the 32th year of publication of *Basic & Clinical Pharmacology.* The widespread adoption of the first twelve editions indicates that this book fills an important need. We believe that the thirteenth edition will satisfy this need even more successfully. Spanish, Portuguese, Italian, French, Indonesian, Japanese, Korean, Turkish, and Ukrainian translations are available. Translations into other languages are under way; the publisher may be contacted for further information.

I wish to acknowledge the prior and continuing efforts of my contributing authors and the major contributions of the staff at Lange Medical Publications, Appleton & Lange, and McGraw-Hill, and of our editors for this edition, Donna Frassetto and Rachel D'Annucci Henriquez. I also wish to thank Alice Camp and Katharine Katzung for their expert proofreading contributions.

Suggestions and comments about *Basic & Clinical Pharmacology* are always welcome. They may be sent to me in care of the publisher.

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San Francisco
December, 2011

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SECTION I BASIC PRINCIPLES

CHAPTER 1

Introduction: The Nature of Drugs & Drug Development & Regulation

Bertram G. Katzung, MD, PhD*

CASE STUDY

A 26-year-old man is brought by friends to the emergency department of the city hospital because he has been behaving strangely for several days. A known user of methamphetamine, he has not eaten or slept in 48 hours. He threatened to shoot one of his friends because he believes this friend is plotting against him. On admission, the man is extremely agitated, appears to be underweight, and is unable to give a coherent history. He has to be restrained to prevent him from walking out of the emergency department and into traffic on the street. His blood pressure is 160/100 mm Hg, heart rate 100, temperature 39°C, and respirations 30/min. His arms show evidence of numerous intravenous injections. The remainder of his physical examination is unremarkable. After evaluation, the man is given a sedative, fluids, a diuretic, and ammonium chloride parenterally. What is the purpose of the ammonium chloride?

Pharmacology can be defined as the study of substances that interact with living systems through chemical processes, especially by binding to regulatory molecules and activating or inhibiting normal body processes. These substances may be chemicals administered to achieve a beneficial therapeutic effect on some process within the patient or for their toxic effects on regulatory processes in parasites infecting the patient. Such deliberate therapeutic applications may be considered the proper role of **medical pharmacology,** which is often defined as the science of substances used to prevent, diagnose, and treat disease. **Toxicology** is the branch of pharmacology that deals with the undesirable

*The author thanks Barry Berkowitz, PhD, for contributions to the second part of this chapter.

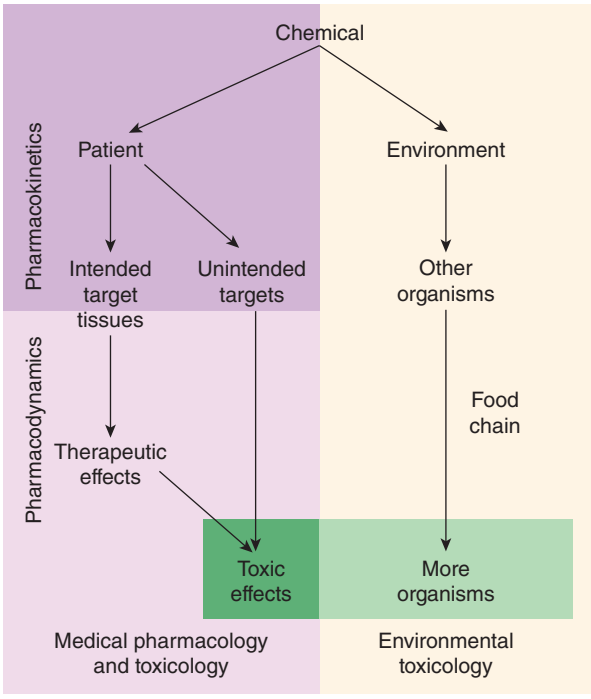


FIGURE 1–1 Major areas of study in pharmacology. The actions of chemicals can be divided into two large domains. The first (*left side*) is that of medical pharmacology and toxicology, which is aimed at understanding the actions of drugs as chemicals on individual organisms, especially humans and domestic animals. Both beneficial and toxic effects are included. Pharmacokinetics deals with the absorption, distribution, and elimination of drugs. Pharmacodynamics concerns the actions of the chemical on the organism. The second domain (*right side*) is that of environmental toxicology, which is concerned with the effects of chemicals on all organisms and their survival in groups and as species.

effects of chemicals on living systems, from individual cells to humans to complex ecosystems (Figure 1–1). The nature of drugs—their physical properties and their interactions with biological systems—is discussed in part I of this chapter. The development of new drugs and their regulation by government agencies are discussed in part II.

THE HISTORY OF PHARMACOLOGY

Prehistoric people undoubtedly recognized the beneficial or toxic effects of many plant and animal materials. Early written records list remedies of many types, including a few that are still recognized as useful drugs today. Most, however, were worthless or actually harmful. In the last 1500 years, sporadic attempts were made to introduce rational methods into medicine, but none was successful owing to the dominance of systems of thought that purported to explain all of biology and disease without the need for experimentation and observation. These schools promulgated bizarre notions such as the idea that disease was caused by excesses of bile or blood in the body, that wounds could be healed by applying a salve to the weapon that caused the wound, and so on.

Around the end of the 17th century, and following the example of the physical sciences, reliance on observation and experimentation began to replace theorizing in medicine. As the value of these methods in the study of disease became clear, physicians in Great Britain and on the Continent began to apply them to the effects of traditional drugs used in their own practices. Thus, **materia medica**—the science of drug preparation and the medical uses of drugs—began to develop as the precursor to pharmacology. However, any real understanding of the mechanisms of action of drugs was prevented by the absence of methods for purifying active agents from the crude materials that were available and—even more—by the lack of methods for testing hypotheses about the nature of drug actions.

In the late 18th and early 19th centuries, François Magendie, and his student Claude Bernard, began to develop the methods of **experimental physiology** and **pharmacology.** Advances in chemistry and the further development of physiology in the 18th, 19th, and early 20th centuries laid the foundation needed for understanding how drugs work at the organ and tissue levels. Paradoxically, real advances in basic pharmacology during this time were accompanied by an outburst of unscientific claims by manufacturers and marketers of worthless "patent medicines." Not until the concepts of rational therapeutics, especially that of the **controlled clinical trial,** were reintroduced into medicine—only about 60 years ago—did it become possible to accurately evaluate therapeutic claims.

Around the same time, a major expansion of research efforts in all areas of biology began. As new concepts and new techniques were introduced, information accumulated about drug action and the biologic substrate of that action, the **drug receptor.** During the last half-century, many fundamentally new drug groups and new members of old groups were introduced. The last three decades have seen an even more rapid growth of information and understanding of the molecular basis for drug action. The molecular mechanisms of action of many drugs have now been identified, and numerous receptors have been isolated, structurally characterized, and cloned. In fact, the use of receptor identification methods (described in Chapter 2) has led to the discovery of many orphan receptors—receptors for which no ligand has been discovered and whose function can only be surmised. Studies of the local molecular environment of receptors have shown that receptors and effectors do not function in isolation; they are strongly influenced by other receptors and by companion regulatory proteins.

Pharmacogenomics—the relation of the individual's genetic makeup to his or her response to specific drugs—is close to becoming an important part of therapeutics (see Chapter 5). Decoding of the genomes of many species—from bacteria to humans—has led to the recognition of unsuspected relationships between receptor families and the ways that receptor proteins have evolved. Discovery that small segments of RNA can interfere with protein synthesis with extreme selectivity has led to investigation of **small interfering RNAs (siRNAs)** and **microRNAs (miRNAs)** as therapeutic agents. Similarly, short nucleotide chains called **antisense oligonucleotides (ANOs),** synthesized to be complementary to natural RNA or DNA, can interfere with the readout of genes and the transcription of RNA. These intracellular targets may provide the next major wave of advances in therapeutics.

The extension of scientific principles into everyday therapeutics is still going on, although the medication-consuming public is still exposed to vast amounts of inaccurate, incomplete, or unscientific information regarding the pharmacologic effects of chemicals. This has resulted in the irrational use of innumerable expensive, ineffective, and sometimes harmful remedies and the growth of a huge "alternative health care" industry. Unfortunately, manipulation of the legislative process in the United States has allowed many substances promoted for health—but not promoted specifically as "drugs"—to avoid meeting the Food and Drug Administration (FDA) standards described in the second part of this chapter. Conversely, lack of understanding of basic scientific principles in biology and statistics and the absence of critical thinking about public health issues have led to rejection of medical science by a segment of the public and to a common tendency to assume that all adverse drug effects are the result of malpractice.

Two general principles that the student should remember are (1) that *all* substances can under certain circumstances be toxic, and the chemicals in botanicals (herbs and plant extracts, "nutraceuticals") are no different from chemicals in manufactured drugs except for the much greater proportion of impurities in botanicals; and (2) that all dietary supplements and all therapies promoted as health-enhancing should meet the same standards of efficacy and safety as conventional drugs and medical therapies. That is, there should be no artificial separation between scientific medicine and "alternative" or "complementary" medicine. Ideally, all nutritional and botanical substances should be tested by the same randomized controlled trials (RCTs) as synthetic compounds.

I GENERAL PRINCIPLES OF PHARMACOLOGY

THE NATURE OF DRUGS

In the most general sense, a drug may be defined as any substance that brings about a change in biologic function through its chemical actions. In most cases, the drug molecule interacts as an **agonist** (activator) or **antagonist** (inhibitor) with a specific molecule in the biologic system that plays a regulatory role. This target molecule is called a **receptor**. The nature of receptors is discussed more fully in Chapter 2. In a very small number of cases, drugs known as **chemical antagonists** may interact directly with other drugs, whereas a few drugs (osmotic agents) interact almost exclusively with water molecules. Drugs may be synthesized within the body (eg, **hormones**) or may be chemicals *not* synthesized in the body (ie, **xenobiotics,** from the Greek *xenos*, meaning "stranger"). **Poisons** are drugs that have almost exclusively harmful effects. However, Paracelsus (1493–1541) famously stated that "the dose makes the poison," meaning that any substance can be harmful if taken in the wrong dosage. **Toxins** are usually defined as poisons of biologic origin, ie, synthesized by plants or animals, in contrast to inorganic poisons such as lead and arsenic.

To interact chemically with its receptor, a drug molecule must have the appropriate size, electrical charge, shape, and atomic composition. Furthermore, a drug is often administered at a location distant from its intended site of action, eg, a pill given orally to relieve a headache. Therefore, a useful drug must have the necessary properties to be transported from its site of administration to its site of action. Finally, a practical drug should be inactivated or excreted from the body at a reasonable rate so that its actions will be of appropriate duration.

The Physical Nature of Drugs

Drugs may be solid at room temperature (eg, aspirin, atropine), liquid (eg, nicotine, ethanol), or gaseous (eg, nitrous oxide). These factors often determine the best route of administration. The most common routes of administration are described in Table 3–3. The various classes of organic compounds—carbohydrates, proteins, lipids, and their constituents—are all represented in pharmacology. As noted above, oligonucleotides, in the form of small segments of RNA, have entered clinical trials and are on the threshold of introduction into therapeutics.

A number of useful or dangerous drugs are inorganic elements, eg, lithium, iron, and heavy metals. Many organic drugs are weak acids or bases. This fact has important implications for the way they are handled by the body, because pH differences in the various compartments of the body may alter the degree of ionization of such drugs (see text that follows).

Drug Size

The molecular size of drugs varies from very small (lithium ion, MW 7) to very large (eg, alteplase [t-PA], a protein of MW 59,050). However, most drugs have molecular weights between 100 and 1000. The lower limit of this narrow range is probably set by the requirements for specificity of action. To have a good "fit" to only one type of receptor, a drug molecule must be sufficiently unique in shape, charge, and other properties, to prevent its binding to other receptors. To achieve such selective binding, it appears that a molecule should in most cases be at least 100 MW units in size. The upper limit in molecular weight is determined primarily by the requirement that drugs must be able to move within the body (eg, from the site of administration to the site of action). Drugs much larger than MW 1000 do not diffuse readily between compartments of the body (see Permeation, in following text). Therefore, very large drugs (usually proteins) must often be administered directly into the compartment where they have their effect. In the case of alteplase, a clot-dissolving enzyme, the drug is administered directly into the vascular compartment by intravenous or intra-arterial infusion.

Drug Reactivity & Drug-Receptor Bonds

Drugs interact with receptors by means of chemical forces or bonds. These are of three major types: **covalent, electrostatic,** and **hydrophobic.** Covalent bonds are very strong and in many cases not reversible under biologic conditions. Thus, the covalent bond formed between the acetyl group of acetylsalicylic acid (aspirin) and cyclooxygenase, its enzyme target in platelets, is not readily broken. The platelet aggregation–blocking effect of aspirin lasts

long after free acetylsalicylic acid has disappeared from the bloodstream (about 15 minutes) and is reversed only by the synthesis of new enzyme in new platelets, a process that takes several days. Other examples of highly reactive, covalent bond-forming drugs include the DNA-alkylating agents used in cancer chemotherapy to disrupt cell division in the tumor.

Electrostatic bonding is much more common than covalent bonding in drug-receptor interactions. Electrostatic bonds vary from relatively strong linkages between permanently charged ionic molecules to weaker hydrogen bonds and very weak induced dipole interactions such as van der Waals forces and similar phenomena. Electrostatic bonds are weaker than covalent bonds.

Hydrophobic bonds are usually quite weak and are probably important in the interactions of highly lipid-soluble drugs with the lipids of cell membranes and perhaps in the interaction of drugs with the internal walls of receptor "pockets."

The specific nature of a particular drug-receptor bond is of less practical importance than the fact that drugs that bind through weak bonds to their receptors are generally more selective than drugs that bind by means of very strong bonds. This is because weak bonds require a very precise fit of the drug to its receptor if an interaction is to occur. Only a few receptor types are likely to provide such a precise fit for a particular drug structure. Thus, if we wished to design a highly selective short-acting drug for a particular receptor, we would avoid highly reactive molecules that form covalent bonds and instead choose a molecule that forms weaker bonds.

A few substances that are almost completely inert in the chemical sense nevertheless have significant pharmacologic effects. For example, xenon, an "inert" gas, has anesthetic effects at elevated pressures.

Drug Shape

The shape of a drug molecule must be such as to permit binding to its receptor site via the bonds just described. Optimally, the drug's shape is complementary to that of the receptor site in the same way that a key is complementary to a lock. Furthermore, the phenomenon of **chirality (stereoisomerism)** is so common in biology that more than half of all useful drugs are chiral molecules; that is, they can exist as enantiomeric pairs. Drugs with two asymmetric centers have four diastereomers, eg, ephedrine, a sympathomimetic drug. In most cases, one of these enantiomers is much more potent than its mirror image enantiomer, reflecting a better fit to the receptor molecule. If one imagines the receptor site to be like a glove into which the drug molecule must fit to bring about its effect, it is clear why a "left-oriented" drug is more effective in binding to a left-hand receptor than its "right-oriented" enantiomer.

The more active enantiomer at one type of receptor site may not be more active at another receptor type, eg, a type that may be responsible for some other effect. For example, carvedilol, a drug that interacts with adrenoceptors, has a single chiral center and thus two enantiomers (Table 1–1). One of these enantiomers, the *(S)*(–) isomer, is a potent β-receptor blocker. The *(R)*(+) isomer is 100-fold weaker at the β receptor. However, the isomers are approximately equipotent as α-receptor blockers. Ketamine is an intravenous anesthetic. The (+) enantiomer is a more potent anesthetic and is less toxic than the (–) enantiomer. Unfortunately, the drug is still used as the racemic mixture.

TABLE 1–1 Dissociation constants (K_d) of the enantiomers and racemate of carvedilol.

Form of Carvedilol	α Receptors (K_d, nmol/L[1])	β Receptors (K_d, nmol/L)
R(+) enantiomer	14	45
S(–) enantiomer	16	0.4
R,S(±) enantiomers	11	0.9

[1]The K_d is the concentration for 50% saturation of the receptors and is inversely proportionate to the affinity of the drug for the receptors.

Data from Ruffolo RR et al: The pharmacology of carvedilol. Eur J Clin Pharmacol 1990;38:S82.

Finally, because enzymes are usually stereoselective, one drug enantiomer is often more susceptible than the other to drug-metabolizing enzymes. As a result, the duration of action of one enantiomer may be quite different from that of the other. Similarly, drug transporters may be stereoselective.

Unfortunately, most studies of clinical efficacy and drug elimination in humans have been carried out with racemic mixtures of drugs rather than with the separate enantiomers. At present, only a small percentage of the chiral drugs used clinically are marketed as the active isomer—the rest are available only as racemic mixtures. As a result, many patients are receiving drug doses of which 50% is less active, inactive, or actively toxic. Some drugs are currently available in both the racemic and the pure, active isomer forms. Unfortunately, the hope that administration of the pure, active enantiomer would decrease adverse effects relative to those produced by racemic formulations has not been established.

Rational Drug Design

Rational design of drugs implies the ability to predict the appropriate molecular structure of a drug on the basis of information about its biologic receptor. Until recently, no receptor was known in sufficient detail to permit such drug design. Instead, drugs were developed through random testing of chemicals or modification of drugs already known to have some effect. However, the characterization of many receptors during the past three decades has changed this picture. A few drugs now in use were developed through molecular design based on knowledge of the three-dimensional structure of the receptor site. Computer programs are now available that can iteratively optimize drug structures to fit known receptors. As more becomes known about receptor structure, rational drug design will become more common.

Receptor Nomenclature

The spectacular success of newer, more efficient ways to identify and characterize receptors (see Chapter 2) has resulted in a variety of differing, and sometimes confusing, systems for naming them. This in turn has led to a number of suggestions regarding more rational methods of naming receptors. The interested reader is

referred for details to the efforts of the International Union of Pharmacology (IUPHAR) *Committee on Receptor Nomenclature and Drug Classification* (reported in various issues of *Pharmacological Reviews* and elsewhere) and to Alexander SPH, Mathie A, Peters JA: Guide to receptors and channels (GRAC), 5th edition. *Br J Pharmacol* 2011;164(Suppl 1):S1–S324. The chapters in this book mainly use these sources for naming receptors.

DRUG-BODY INTERACTIONS

The interactions between a drug and the body are conveniently divided into two classes. The actions of the drug on the body are termed **pharmacodynamic** processes (Figure 1–1); the principles of pharmacodynamics are presented in greater detail in Chapter 2. These properties determine the group in which the drug is classified, and they play the major role in deciding whether that group is appropriate therapy for a particular symptom or disease. The actions of the body on the drug are called **pharmacokinetic** processes and are described in Chapters 3 and 4. Pharmacokinetic processes govern the absorption, distribution, and elimination of drugs and are of great practical importance in the choice and administration of a particular drug for a particular patient, eg, a patient with impaired renal function. The following paragraphs provide a brief introduction to pharmacodynamics and pharmacokinetics.

Pharmacodynamic Principles

Most drugs must bind to a receptor to bring about an effect. However, at the cellular level, drug binding is only the first in a sequence of steps:

- Drug (D) + receptor-effector (R) → drug-receptor-effector complex → effect
- D + R → drug-receptor complex → effector molecule → effect
- D + R → D-R complex → activation of coupling molecule → effector molecule → effect
- Inhibition of metabolism of endogenous activator → increased activator action on an effector molecule → increased effect

Note that the final change in function is accomplished by an **effector** mechanism. The effector may be part of the receptor molecule or may be a separate molecule. A very large number of receptors communicate with their effectors through coupling molecules, as described in Chapter 2.

A. Types of Drug-Receptor Interactions

Agonist drugs bind to and *activate* the receptor in some fashion, which directly or indirectly brings about the effect (Figure 1–2A). Receptor activation involves a change in conformation in the cases that have been studied at the molecular structure level. Some receptors incorporate effector machinery in the same molecule, so that drug binding brings about the effect directly, eg, opening of an ion channel or activation of enzyme activity. Other receptors are linked through one or more intervening coupling molecules to a separate effector molecule. The five major types of drug-receptor-effector coupling systems are discussed in Chapter 2.

Pharmacologic antagonist drugs, by binding to a receptor, compete with and prevent binding by other molecules. For example, acetylcholine receptor blockers such as atropine are antagonists because they prevent access of acetylcholine and similar agonist drugs to the acetylcholine receptor site and they stabilize the receptor in its inactive state (or some state other than the acetylcholine-activated state). These agents reduce the effects of acetylcholine and similar molecules in the body (Figure 1–2B), but their action can be overcome by increasing the dosage of agonist. Some antagonists bind very tightly to the receptor site in an irreversible or pseudoirreversible fashion and cannot be displaced by increasing the agonist concentration. Drugs that bind to the same receptor molecule but do not prevent binding of the agonist are said to act **allosterically** and may enhance (Figure 1–2C) or inhibit (Figure 1–2D) the action of the agonist molecule. Allosteric inhibition is not overcome by increasing the dose of agonist.

B. Agonists That Inhibit Their Binding Molecules

Some drugs mimic agonist drugs by inhibiting the molecules responsible for terminating the action of an endogenous agonist. For example, acetylcholinesterase *inhibitors*, by slowing the destruction of endogenous acetylcholine, cause cholinomimetic effects that closely resemble the actions of cholinoceptor *agonist* molecules even though cholinesterase inhibitors do not bind or only incidentally bind to cholinoceptors (see Chapter 7). Because they amplify the effects of physiologically released agonist ligands, their effects are sometimes more selective and less toxic than those of exogenous agonists.

C. Agonists, Partial Agonists, and Inverse Agonists

Figure 1–3 describes a useful model of drug-receptor interaction. As indicated, the receptor is postulated to exist in the inactive, nonfunctional form (R_i) and in the activated form (R_a). Thermodynamic considerations indicate that even in the absence of any agonist, some of the receptor pool must exist in the R_a form some of the time and may produce the same physiologic effect as agonist-induced activity. This effect, occurring in the absence of agonist, is termed **constitutive activity.** Agonists have a much higher affinity for the R_a configuration and stabilize it, so that a large percentage of the total pool resides in the R_a–D fraction and a large effect is produced. The recognition of constitutive activity may depend on the receptor density, the concentration of coupling molecules (if a coupled system), and the number of effectors in the system.

Many agonist drugs, when administered at concentrations sufficient to saturate the receptor pool, can activate their receptor-effector systems to the maximum extent of which the system is capable; that is, they cause a shift of almost all of the receptor pool to the R_a–D pool. Such drugs are termed **full agonists.** Other drugs, called **partial agonists,** bind to the same receptors and activate them in the same way but do not evoke as great a response, no matter how high the concentration. In the model in Figure 1–3, partial agonists do not stabilize the R_a configuration as fully as full agonists, so that a significant fraction of receptors exists in the R_i–D pool. Such drugs are said to have low **intrinsic efficacy.**

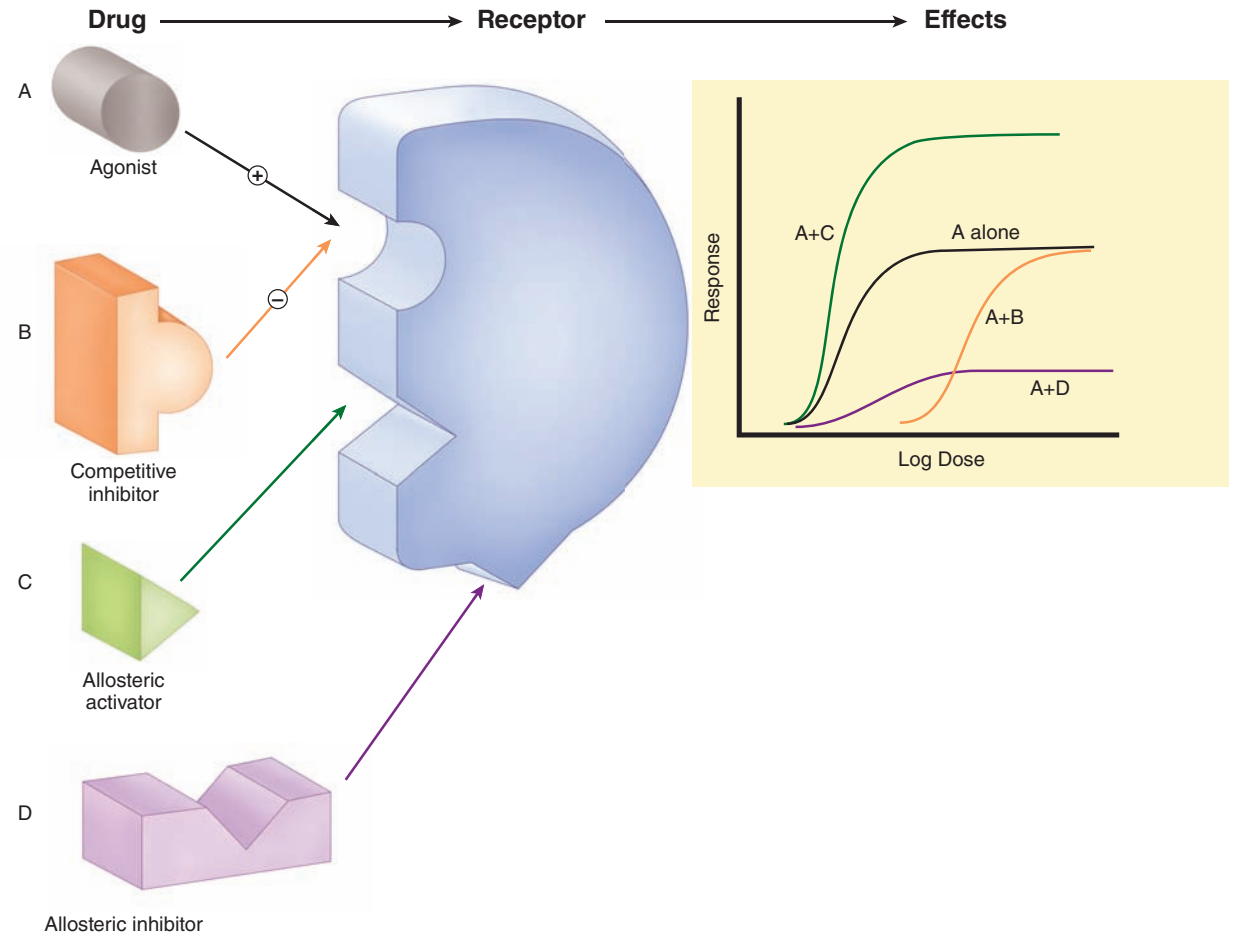


FIGURE 1–2 Drugs may interact with receptors in several ways. The effects resulting from these interactions are diagrammed in the dose-response curves at the right. Drugs that alter the agonist (**A**) response may activate the agonist binding site, compete with the agonist (competitive inhibitors, **B**), or act at separate (allosteric) sites, increasing (**C**) or decreasing (**D**) the response to the agonist. Allosteric activators (**C**) may increase the efficacy of the agonist or its binding affinity. The curve shown reflects an increase in efficacy; an increase in affinity would result in a leftward shift of the curve.

Thus, pindolol, a β-adrenoceptor partial agonist, may act either as an agonist (if no full agonist is present) or as an antagonist (if a full agonist such as epinephrine is present). (See Chapter 2.) Intrinsic efficacy is independent of affinity (as usually measured) for the receptor.

In the same model, conventional antagonist action can be explained as fixing the fractions of drug-bound R_i and R_a in the same relative amounts as in the absence of any drug. In this situation, no change in activity will be observed, so the drug will appear to be without effect. However, the presence of the antagonist at the receptor site will block access of agonists to the receptor and prevent the usual agonist effect. Such blocking action can be termed **neutral antagonism.**

What will happen if a drug has a much stronger affinity for the R_i than for the R_a state and stabilizes a large fraction in the R_i–D pool? In this scenario the drug will reduce any constitutive activity, thus resulting in effects that are the opposite of the effects produced by conventional agonists at that receptor. Such drugs are termed **inverse agonists** (Figure 1–3). One of the best documented examples of such a system is the γ-aminobutyric acid ($GABA_A$) receptor-effector (a chloride channel) in the nervous system. This receptor is activated by the endogenous transmitter GABA and causes inhibition of postsynaptic cells. Conventional exogenous agonists such as benzodiazepines also facilitate the receptor-effector system and cause GABA-like inhibition with sedation as the therapeutic result. This sedation can be reversed by conventional neutral antagonists such as flumazenil. Inverse agonists of this receptor system cause anxiety and agitation, the inverse of sedation (see Chapter 22). Similar inverse agonists have been found for β adrenoceptors, histamine H_1 and H_2 receptors, and several other receptor systems.

D. Duration of Drug Action

Termination of drug action is a result of one of several processes. In some cases, the effect lasts only as long as the drug occupies the receptor, and dissociation of drug from the receptor automatically terminates the effect. In many cases, however, the action may persist after the drug has dissociated because, for example, some coupling molecule is still present in activated form. In the case of drugs that bind covalently to the receptor site, the effect may persist until the drug-receptor complex is destroyed and new receptors or enzymes are synthesized, as described previously for aspirin. In addition, many receptor-effector systems incorporate

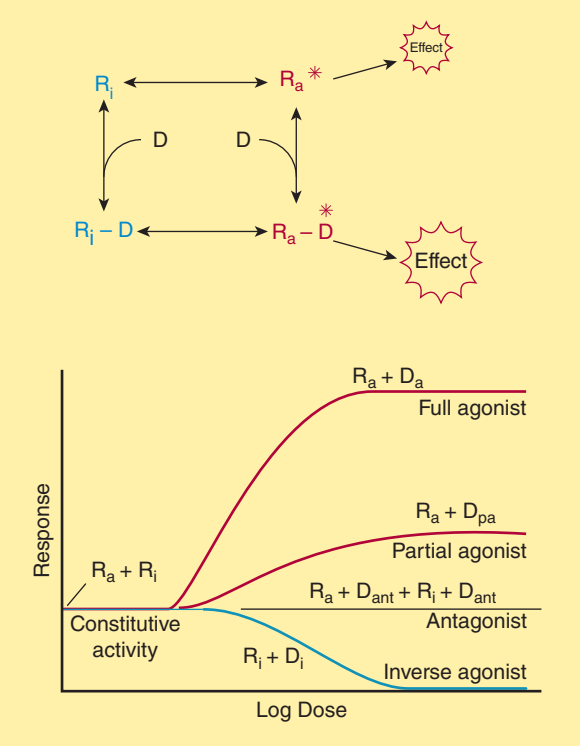


FIGURE 1–3 A model of drug-receptor interaction. The receptor is able to assume two conformations. In the R_i conformation, it is inactive and produces no effect, even when combined with a drug molecule. In the R_a conformation, the receptor can activate downstream mechanisms that produce a small observable effect, even in the absence of drug (constitutive activity). In the absence of drugs, the two isoforms are in equilibrium, and the R_i form is favored. Conventional full agonist drugs have a much higher affinity for the R_a conformation, and mass action thus favors the formation of the R_a–D complex with a much larger observed effect. Partial agonists have an intermediate affinity for both R_i and R_a forms. Conventional antagonists, according to this hypothesis, have equal affinity for both receptor forms and maintain the same level of constitutive activity. Inverse agonists, on the other hand, have a much higher affinity for the R_i form, reduce constitutive activity, and may produce a contrasting physiologic result.

desensitization mechanisms for preventing excessive activation when agonist molecules continue to be present for long periods. (See Chapter 2 for additional details.)

E. Receptors and Inert Binding Sites

To function as a receptor, an endogenous molecule must first be **selective** in choosing ligands (drug molecules) to bind; and second, it must **change its function** upon binding in such a way that the function of the biologic system (cell, tissue, etc) is altered. The selectivity characteristic is required to avoid constant activation of the receptor by promiscuous binding of many different ligands. The ability to change function is clearly necessary if the ligand is to cause a pharmacologic effect. The body contains a vast array of molecules that are capable of binding drugs, however, and not all of these endogenous molecules are regulatory molecules. Binding of a drug to a nonregulatory molecule such as plasma albumin will result in no detectable change in the function of the biologic system, so this endogenous molecule can be called an **inert binding site.** Such binding is not completely without significance, however, because it affects the distribution of drug within the body and determines the amount of free drug in the circulation. Both of these factors are of pharmacokinetic importance (see also Chapter 3).

Pharmacokinetic Principles

In practical therapeutics, a drug should be able to reach its intended site of action after administration by some convenient route. In many cases, the active drug molecule is sufficiently lipid-soluble and stable to be given as such. In some cases, however, an inactive precursor chemical that is readily absorbed and distributed must be administered and then converted to the active drug by biologic processes—inside the body. Such a precursor chemical is called a **prodrug.**

In only a few situations is it possible to apply a drug directly to its target tissue, eg, by topical application of an anti-inflammatory agent to inflamed skin or mucous membrane. Most often, a drug is administered into one body compartment, eg, the gut, and must move to its site of action in another compartment, eg, the brain in the case of an antiseizure medication. This requires that the drug be **absorbed** into the blood from its site of administration and **distributed** to its site of action, **permeating** through the various barriers that separate these compartments. For a drug given orally to produce an effect in the central nervous system, these barriers include the tissues that make up the wall of the intestine, the walls of the capillaries that perfuse the gut, and the blood-brain barrier, the walls of the capillaries that perfuse the brain. Finally, after bringing about its effect, a drug should be **eliminated** at a reasonable rate by metabolic inactivation, by excretion from the body, or by a combination of these processes.

A. Permeation

Drug permeation proceeds by several mechanisms. Passive diffusion in an aqueous or lipid medium is common, but active processes play a role in the movement of many drugs, especially those whose molecules are too large to diffuse readily (Figure 1–4). Drug **vehicles** can be very important in facilitating transport and permeation, eg, by encapsulating the active agent in liposomes and in regulating release, as in slow release preparations. Newer methods of facilitating transport of drugs by coupling them to **nanoparticles** are under investigation.

1. ***Aqueous diffusion***—Aqueous diffusion occurs within the larger aqueous compartments of the body (interstitial space, cytosol, etc) and across epithelial membrane tight junctions and the endothelial lining of blood vessels through aqueous pores that—in some tissues—permit the passage of molecules as large as MW 20,000–30,000.* See Figure 1–4A.

*The capillaries of the brain, the testes, and some other tissues are characterized by the absence of pores that permit aqueous diffusion. They may also contain high concentrations of drug export pumps (MDR pumps; see text). These tissues are therefore protected or "sanctuary" sites from many circulating drugs.

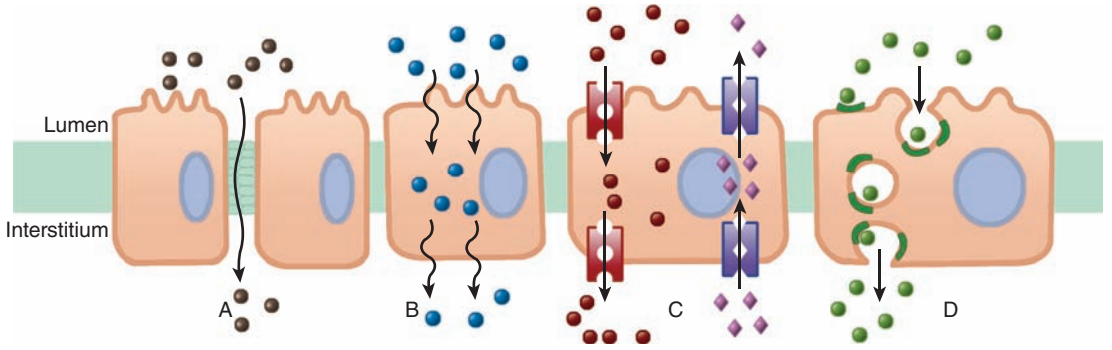


FIGURE 1–4 Mechanisms of drug permeation. Drugs may diffuse passively through aqueous channels in the intercellular junctions (eg, tight junctions, **A**), or through lipid cell membranes (**B**). Drugs with the appropriate characteristics may be transported by carriers into or out of cells (**C**). Very impermeant drugs may also bind to cell surface receptors (dark binding sites), be engulfed by the cell membrane (endocytosis), and then released inside the cell or expelled via the membrane-limited vesicles out of the cell into the extracellular space (exocytosis, **D**).

Aqueous diffusion of drug molecules is usually driven by the concentration gradient of the permeating drug, a downhill movement described by Fick's law (see below). Drug molecules that are bound to large plasma proteins (eg, albumin) do not permeate most vascular aqueous pores. If the drug is charged, its flux is also influenced by electrical fields (eg, the membrane potential and—in parts of the nephron—the transtubular potential).

2. ***Lipid diffusion***—Lipid diffusion is the most important limiting factor for drug permeation because of the large number of lipid barriers that separate the compartments of the body. Because these lipid barriers separate aqueous compartments, the **lipid:aqueous partition coefficient** of a drug determines how readily the molecule moves between aqueous and lipid media. In the case of weak acids and weak bases (which gain or lose electrical charge-bearing protons, depending on the pH), the ability to move from aqueous to lipid or vice versa varies with the pH of the medium, because charged molecules attract water molecules. The ratio of lipid-soluble form to water-soluble form for a weak acid or weak base is expressed by the Henderson-Hasselbalch equation (described in the following text). See Figure 1–4B.
3. ***Special carriers***—Special carrier molecules exist for many substances that are important for cell function and too large or too insoluble in lipid to diffuse passively through membranes, eg, peptides, amino acids, and glucose. These carriers bring about movement by active transport or facilitated diffusion and, unlike passive diffusion, are selective, saturable, and inhibitable. Because many drugs are or resemble such naturally occurring peptides, amino acids, or sugars, they can use these carriers to cross membranes. See Figure 1–4C.

   Many cells also contain less selective membrane carriers that are specialized for expelling foreign molecules. One large family of such transporters binds adenosine triphosphate (ATP) and is called the ABC (ATP-binding cassette) family. This family includes the **P-glycoprotein** or **multidrug resistance type 1 (MDR1) transporter** found in the brain, testes, and other tissues, and in some drug-resistant neoplastic cells, Table 1–2. Similar transport molecules from the ABC family, the **multidrug resistance-associated protein (MRP)** transporters, play important roles in the excretion of some drugs or their metabolites into urine and bile and in the resistance of some tumors to chemotherapeutic drugs. Several other transporter families have been identified that do not bind ATP but use ion gradients to drive transport. Some of these (the solute carrier [SLC] family) are particularly important in the uptake of neurotransmitters across nerve-ending membranes. The latter carriers are discussed in more detail in Chapter 6.
4. ***Endocytosis and exocytosis***—A few substances are so large or impermeant that they can enter cells only by endocytosis, the process by which the substance is bound at a cell-surface receptor, engulfed by the cell membrane, and carried into the cell by pinching off of the newly formed vesicle inside the membrane. The substance can then be released inside the cytosol by breakdown of the vesicle membrane, Figure 1–4D. This process is responsible for the transport of vitamin B_{12}, complexed with a binding protein (intrinsic factor) across the wall of the gut into the blood. Similarly, iron is transported into hemoglobin-synthesizing red blood cell precursors in association with the protein transferrin. Specific receptors for the transport proteins must be present for this process to work.

   The reverse process (exocytosis) is responsible for the secretion of many substances from cells. For example, many neurotransmitter substances are stored in membrane-bound vesicles in nerve endings to protect them from metabolic destruction in the cytoplasm. Appropriate activation of the nerve ending causes fusion of the storage vesicle with the cell membrane and expulsion of its contents into the extracellular space (see Chapter 6).

B. Fick's Law of Diffusion

The passive flux of molecules down a concentration gradient is given by Fick's law:

$$\text{Flux (molecules per unit time)} = (C_1 - C_2) \times \frac{\text{Area} \times \text{Permeability coefficient}}{\text{Thickness}}$$

TABLE 1–2 Some transport molecules important in pharmacology.

Transporter	Physiologic Function	Pharmacologic Significance
NET	Norepinephrine reuptake from synapse	Target of cocaine and some tricyclic antidepressants
SERT	Serotonin reuptake from synapse	Target of selective serotonin reuptake inhibitors and some tricyclic antidepressants
VMAT	Transport of dopamine and norepinephrine into adrenergic vesicles in nerve endings	Target of reserpine and tetrabenazine
MDR1	Transport of many xenobiotics out of cells	Increased expression confers resistance to certain anticancer drugs; inhibition increases blood levels of digoxin
MRP1	Leukotriene secretion	Confers resistance to certain anticancer and antifungal drugs

MDR1, multidrug resistance protein-1; MRP1, multidrug resistance-associated protein-1; NET, norepinephrine transporter; SERT, serotonin reuptake transporter; VMAT, vesicular monoamine transporter.

where C_1 is the higher concentration, C_2 is the lower concentration, area is the cross-sectional area of the diffusion path, permeability coefficient is a measure of the mobility of the drug molecules in the medium of the diffusion path, and thickness is the length of the diffusion path. In the case of lipid diffusion, the lipid:aqueous partition coefficient is a major determinant of mobility of the drug because it determines how readily the drug enters the lipid membrane from the aqueous medium.

C. Ionization of Weak Acids and Weak Bases; the Henderson-Hasselbalch Equation

The electrostatic charge of an ionized molecule attracts water dipoles and results in a polar, relatively water-soluble and lipid-insoluble complex. Because lipid diffusion depends on relatively high lipid solubility, ionization of drugs may markedly reduce their ability to permeate membranes. A very large percentage of the drugs in use are weak acids or weak bases; Table 1–3 lists some examples. For drugs, a weak acid is best defined as a neutral molecule that can reversibly dissociate into an anion (a negatively charged molecule) and a proton (a hydrogen ion). For example, aspirin dissociates as follows:

$$C_8H_7O_2COOH \rightleftharpoons C_8H_7O_2COO^- + H^+$$

Neutral aspirin — Aspirin anion — Proton

A weak base can be defined as a neutral molecule that can form a cation (a positively charged molecule) by combining with a proton. For example, pyrimethamine, an antimalarial drug, undergoes the following association-dissociation process:

$$C_{12}H_{11}ClN_3NH_3^+ \rightleftharpoons C_{12}H_{11}ClN_3NH_2 + H^+$$

Pyrimethamine cation — Neutral pyrimethamine — Proton

Note that the protonated form of a weak acid is the neutral, more lipid-soluble form, whereas the unprotonated form of a weak base is the neutral form. The law of mass action requires that these reactions move to the left in an acid environment (low pH, excess protons available) and to the right in an alkaline environment. The Henderson-Hasselbalch equation relates the ratio of protonated to unprotonated weak acid or weak base to the molecule's pK_a and the pH of the medium as follows:

$$\log \frac{(\text{Protonated})}{(\text{Unprotonated})} = pK_a - pH$$

This equation applies to both acidic and basic drugs. Inspection confirms that the lower the pH relative to the pK_a, the greater will be the fraction of drug in the protonated form. Because the uncharged form is the more lipid-soluble, more of a weak acid will be in the lipid-soluble form at acid pH, whereas more of a basic drug will be in the lipid-soluble form at alkaline pH.

Application of this principle is made in the manipulation of drug excretion by the kidney. Almost all drugs are filtered at the glomerulus. If a drug is in a lipid-soluble form during its passage down the renal tubule, a significant fraction will be reabsorbed by simple passive diffusion. If the goal is to accelerate excretion of the drug (eg, in a case of drug overdose), it is important to prevent its reabsorption from the tubule. This can often be accomplished by adjusting urine pH to make certain that most of the drug is in the ionized state, as shown in Figure 1–5. As a result of this partitioning effect, the drug is "trapped" in the urine. Thus, weak acids are usually excreted faster in alkaline urine; weak bases are usually excreted faster in acidic urine. Other body fluids in which pH differences from blood pH may cause trapping or reabsorption are the contents of the stomach and small intestine, breast milk, aqueous humor, and vaginal and prostatic secretions.

As suggested by Table 1–3, a large number of drugs are weak bases. Most of these bases are amine-containing molecules. The nitrogen of a neutral amine has three atoms associated with it plus a pair of unshared electrons (see the display that follows). The three atoms may consist of one carbon (designated "R") and two hydrogens (a **primary amine**), two carbons and one hydrogen (a **secondary amine**), or three carbon atoms (a **tertiary amine**). Each of these three forms may reversibly bind a proton with the unshared electrons. Some drugs have a fourth carbon-nitrogen bond; these are **quaternary amines**. However, the quaternary amine is permanently charged and has no unshared electrons with which to reversibly bind a proton. Therefore, primary, secondary, and tertiary amines may undergo reversible protonation and vary

TABLE 1–3 Ionization constants of some common drugs.

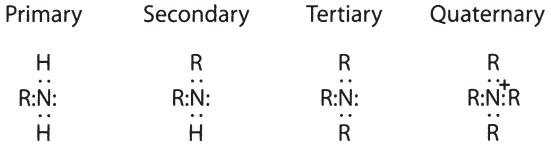
Drug	pK_a[1]	Drug	pK_a[1]	Drug	pK_a[1]
Weak acids		**Weak bases**		**Weak bases (cont'd)**	
Acetaminophen	9.5	Albuterol (salbutamol)	9.3	Isoproterenol	8.6
Acetazolamide	7.2	Allopurinol	9.4, 12.3[2]	Lidocaine	7.9
Ampicillin	2.5	Alprenolol	9.6	Metaraminol	8.6
Aspirin	3.5	Amiloride	8.7	Methadone	8.4
Chlorothiazide	6.8, 9.4[2]	Amiodarone	6.6	Methamphetamine	10.0
Chlorpropamide	5.0	Amphetamine	9.8	Methyldopa	10.6
Ciprofloxacin	6.1, 8.7[2]	Atropine	9.7	Metoprolol	9.8
Cromolyn	2.0	Bupivacaine	8.1	Morphine	7.9
Ethacrynic acid	2.5	Chlordiazepoxide	4.6	Nicotine	7.9, 3.1[2]
Furosemide	3.9	Chloroquine	10.8, 8.4	Norepinephrine	8.6
Ibuprofen	4.4, 5.2[2]	Chlorpheniramine	9.2	Pentazocine	7.9
Levodopa	2.3	Chlorpromazine	9.3	Phenylephrine	9.8
Methotrexate	4.8	Clonidine	8.3	Physostigmine	7.9, 1.8[2]
Methyldopa	2.2, 9.2[2]	Cocaine	8.5	Pilocarpine	6.9, 1.4[2]
Penicillamine	1.8	Codeine	8.2	Pindolol	8.6
Pentobarbital	8.1	Cyclizine	8.2	Procainamide	9.2
Phenobarbital	7.4	Desipramine	10.2	Procaine	9.0
Phenytoin	8.3	Diazepam	3.0	Promethazine	9.1
Propylthiouracil	8.3	Diphenhydramine	8.8	Propranolol	9.4
Salicylic acid	3.0	Diphenoxylate	7.1	Pseudoephedrine	9.8
Sulfadiazine	6.5	Ephedrine	9.6	Pyrimethamine	7.0–7.3[3]
Sulfapyridine	8.4	Epinephrine	8.7	Quinidine	8.5, 4.4[2]
Theophylline	8.8	Ergotamine	6.3	Scopolamine	8.1
Tolbutamide	5.3	Fluphenazine	8.0, 3.9[2]	Strychnine	8.0, 2.3[2]
Warfarin	5.0	Hydralazine	7.1	Terbutaline	10.1
		Imipramine	9.5	Thioridazine	9.5

[1]The pK_a is that pH at which the concentrations of the ionized and nonionized forms are equal.

[2]More than one ionizable group.

[3]Isoelectric point.

their lipid solubility with pH, but quaternary amines are always in the poorly lipid-soluble charged form.



DRUG GROUPS

To learn each pertinent fact about each of the many hundreds of drugs mentioned in this book would be an impractical goal and, fortunately, is unnecessary. Almost all the several thousand drugs currently available can be arranged into about 70 groups. Many of the drugs within each group are very similar in pharmacodynamic actions and in their pharmacokinetic properties as well. For most groups, one or more **prototype drugs** can be identified that typify the most important characteristics of the group. This permits classification of other important drugs in the group as variants of the prototype, so that only the prototype must be learned in detail and, for the remaining drugs, only the differences from the prototype.

II DRUG DEVELOPMENT & REGULATION

A truly new drug (one that does not simply mimic the structure and action of previously available drugs) requires the discovery of a new drug *target*, ie, the pathophysiologic process or substrate of a disease. Such discoveries are usually made in public sector institutions (universities and research institutes), and molecules that have

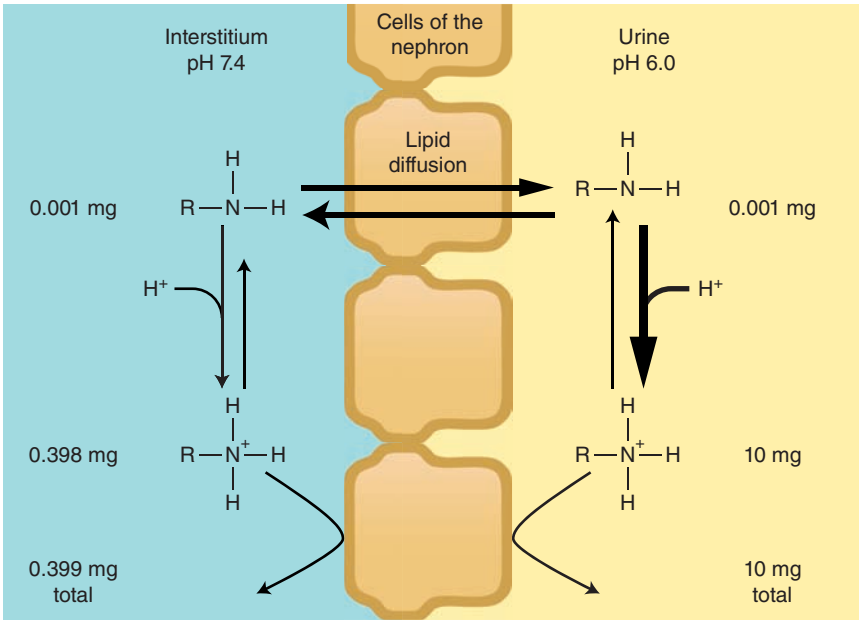


FIGURE 1–5 Trapping of a weak base (methamphetamine) in the urine when the urine is more acidic than the blood. In the hypothetical case illustrated, the diffusible uncharged form of the drug has equilibrated across the membrane, but the total concentration (charged plus uncharged) in the urine (more than 10 mg) is 25 times higher than in the blood (0.4 mg).

beneficial effects on such targets are often discovered in the same laboratories. However, the *development* of new drugs usually takes place in industrial laboratories because optimization of a class of new drugs requires painstaking and expensive chemical, pharmacologic, and toxicologic research. In fact, much of the recent progress in the application of drugs to disease problems can be ascribed to the pharmaceutical industry including "big pharma," the multibillion-dollar corporations that specialize in drug development and marketing. These companies are uniquely skilled in translating basic findings into commercially successful therapeutic breakthroughs.

Such breakthroughs come at a price, however, and the escalating cost of drugs has become a significant contributor to the inflationary increase in the cost of health care. Development of new drugs is enormously expensive, but considerable controversy surrounds drug pricing. Critics claim that the costs of development and marketing are grossly inflated by marketing activities, advertising, and other promotional efforts, which may consume as much as 25% or more of a company's budget. Furthermore, profit margins for big pharma are relatively high. Finally, pricing schedules for many drugs vary dramatically from country to country and even within countries, where large organizations can negotiate favorable prices and small ones cannot. Some countries have already addressed these inequities, and it seems likely that all countries will have to do so during the next few decades.

NEW DRUG DEVELOPMENT

The most common first steps in the development of a new drug are the discovery or synthesis of a potential new drug compound or the elucidation of a new drug target. When a new drug molecule is synthesized or discovered, subsequent steps seek an understanding of the drug's interactions with its biologic targets. Repeated application of this approach leads to compounds with increased efficacy, potency, and selectivity (Figure 1–6). In the United States, the safety and efficacy of drugs must be defined before marketing can be legally carried out. In addition to in vitro studies, relevant biologic effects, drug metabolism, pharmacokinetic profiles, and relative safety of the drug must be characterized in vivo in animals before human drug trials can be started. With regulatory approval, human testing may then go forward (usually in three phases) before the drug is considered for approval for general use. A fourth phase of data gathering and safety monitoring is becoming increasingly important and follows after approval for marketing. Once approved, the great majority of drugs become available for use by any appropriately licensed practitioner. Highly toxic drugs that are nevertheless considered valuable in lethal diseases may be approved for restricted use by practitioners who have undergone special training in their use and who maintain detailed records.

DRUG DISCOVERY

Most new drugs or drug products are discovered or developed through the following approaches: (1) identification or elucidation of a new drug target; (2) rational design of a new molecule based on an understanding of biologic mechanisms and drug receptor structure; (3) screening for biologic activity of large numbers of natural products, banks of previously discovered chemical entities, or large libraries of peptides, nucleic acids, and other organic molecules; and (4) chemical modification of a known active molecule, resulting in a "me-too" analog. Steps (1) and (2) are often carried out in academic research laboratories,

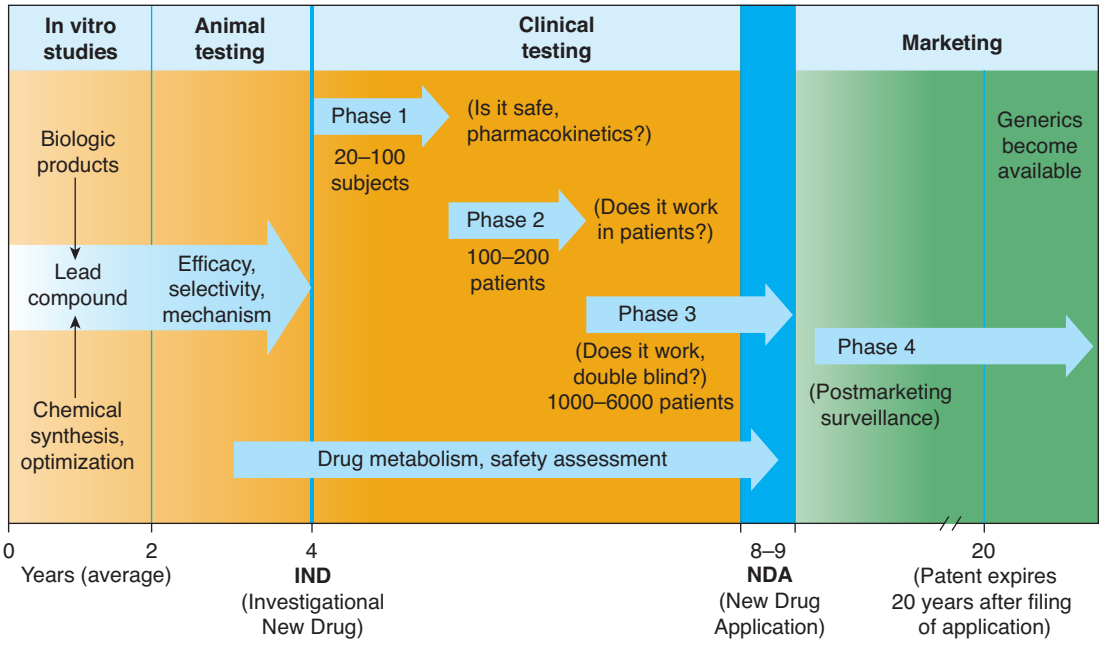


FIGURE 1–6 The development and testing process required to bring a drug to market in the USA. Some of the requirements may be different for drugs used in life-threatening diseases (see text).

but the costs of steps (3) and (4) usually ensure that industry carries them out.

Once a new drug target or promising molecule has been identified, the process of moving from the basic science laboratory to the clinic begins. This **translational research** involves the preclinical and clinical steps described next.

Drug Screening

Drug screening involves a variety of assays at the molecular, cellular, organ system, and whole animal levels to define the **pharmacologic profile**, ie, the activity and selectivity of the drug. The type and number of initial screening tests depend on the pharmacologic and therapeutic goal. For example, anti-infective drugs are tested against a variety of infectious organisms, some of which are resistant to standard agents; hypoglycemic drugs are tested for their ability to lower blood sugar, etc.

The molecule is also studied for a broad array of other actions to determine the mechanism of action and selectivity of the drug. This can reveal both expected and unexpected toxic effects. Occasionally, an unexpected therapeutic action is serendipitously discovered by a careful observer. The selection of compounds for development is most efficiently conducted in animal models of human disease. Where good predictive preclinical models exist (eg, antibacterials, hypertension, or thrombotic disease), we generally have good or excellent drugs. Good drugs or breakthrough improvements are conspicuously lacking and slow for diseases for which preclinical models are poor or not yet available, eg, autism and Alzheimer's disease.

At the molecular level, the compound would be screened for activity on the target, for example, receptor binding affinity to cell membranes containing the homologous animal receptors (or if possible, on the cloned human receptors). Early studies would be done to predict effects that might later cause undesired drug metabolism or toxicologic complications. For example, studies on liver cytochrome P450 enzymes would be performed to determine whether the molecule of interest is likely to be a substrate or inhibitor of these enzymes or to interfere with the metabolism of other drugs.

Effects on cell function determine whether the drug is an agonist, partial agonist, inverse agonist, or antagonist at relevant receptors. Isolated tissues would be used to characterize the pharmacologic activity and selectivity of the new compound in comparison with reference compounds. Comparison with other drugs would also be undertaken in a variety of in vivo studies. At each step in this process, the compound would have to meet specific performance and selectivity criteria to be carried further.

Whole animal studies are generally necessary to determine the effect of the drug on organ systems and disease models. Cardiovascular and renal function studies of new drugs are generally first performed in normal animals. Studies on disease models, if available, are then performed. For a candidate antihypertensive drug, animals with hypertension would be treated to see whether blood pressure was lowered in a dose-related manner and to characterize other effects of the compound. Evidence would be collected on duration of action and efficacy after oral and parenteral administration. If the agent possessed useful activity, it would be further studied for possible adverse effects on other major organs, including the respiratory, gastrointestinal, endocrine, and central nervous systems.

These studies might suggest the need for further chemical modification (compound optimization) to achieve more desirable pharmacokinetic or pharmacodynamic properties. For example, oral administration studies might show that the drug was poorly

absorbed or rapidly metabolized in the liver; modification to improve bioavailability might be indicated. If the drug was to be administered long term, an assessment of tolerance development would be made. For drugs related to or having mechanisms of action similar to those known to cause physical or psychological dependence, abuse potential would also be studied. Drug interactions would be examined.

The desired result of this screening procedure (which may have to be repeated several times with congeners of the original molecule) is a **lead compound**, ie, a leading candidate for a successful new drug. A patent application would be filed for a novel compound (a composition of matter patent) that is efficacious, or for a new and nonobvious therapeutic use (a use patent) for a previously known chemical entity.

PRECLINICAL SAFETY & TOXICITY TESTING

All drugs are toxic in some individuals at some dose. Candidate drugs that survive the initial screening procedures must be carefully evaluated for potential risks before and during clinical testing. Depending on the proposed use of the drug, preclinical toxicity testing includes most or all of the procedures shown in Table 1–4. Although no chemical can be certified as completely "safe" (free of risk), the objective is to estimate the risk associated with exposure to the drug candidate and to consider this in the context of therapeutic needs and likely duration of drug use.

The goals of preclinical toxicity studies include identifying potential human toxicities, designing tests to further define the toxic mechanisms, and predicting the most relevant toxicities to be monitored in clinical trials. In addition to the studies shown in Table 1–4, several quantitative estimates are desirable. These include the **no-effect dose**—the maximum dose at which a specified toxic effect is not seen; the **minimum lethal dose**—the smallest dose that is observed to kill any experimental animal; and, if necessary, the **median lethal dose (LD_{50})**—the dose that kills approximately 50% of the animals. Presently, the LD_{50} is estimated from the smallest number of animals possible. These doses are used to calculate the initial dose to be tried in humans, usually taken as one hundredth to one tenth of the no-effect dose in animals.

It is important to recognize the limitations of preclinical testing. These include the following:

1. Toxicity testing is time-consuming and expensive. Two to 6 years may be required to collect and analyze data on toxicity before the drug can be considered ready for testing in humans.
2. Large numbers of animals may be needed to obtain valid preclinical data. Scientists are properly concerned about this situation, and progress has been made toward reducing the numbers required while still obtaining valid data. Cell and tissue culture in vitro methods and computer modeling are increasingly being used, but their predictive value is still limited. Nevertheless, some segments of the public attempt to halt all animal testing in the unfounded belief that it has become unnecessary.
3. Extrapolations of therapeutic index and toxicity data from animals to humans are reasonably predictive for many but not for all toxicities.
4. For statistical reasons, rare adverse effects are unlikely to be detected in preclinical testing.

EVALUATION IN HUMANS

A very small fraction of lead compounds reach clinical trials and less than one third of the drugs granted INDs survive clinical trials and reach the marketplace. Federal law in the USA and ethical considerations require that the study of new drugs in humans be conducted in accordance with stringent guidelines. Scientifically valid results are not guaranteed simply by conforming to government regulations, however, and the design and execution of a good clinical trial require interdisciplinary personnel including basic scientists, clinical pharmacologists, clinician specialists, statisticians, and others. The need for careful design and execution is based on three major confounding factors inherent in the study of any drug in humans.

TABLE 1–4 Safety tests.

Type of Test	Approach and Goals
Acute toxicity	Usually two species, two routes. Determine the no-effect dose and the maximum tolerated dose. In some cases, determine the acute dose that is lethal in approximately 50% of animals.
Subacute or subchronic toxicity	Three doses, two species. Two weeks to 3 months of testing may be required before clinical trials. The longer the duration of expected clinical use, the longer the subacute test. Determine biochemical, physiologic effects.
Chronic toxicity	Rodent and at least one nonrodent species for ≥ 6 months. Required when drug is intended to be used in humans for prolonged periods. Usually run concurrently with clinical trials. Determine same end points as subacute toxicity tests.
Effect on reproductive performance	Two species, usually one rodent and rabbits. Test effects on animal mating behavior, reproduction, parturition, progeny, birth defects, postnatal development.
Carcinogenic potential	Two years, two species. Required when drug is intended to be used in humans for prolonged periods. Determine gross and histologic pathology.
Mutagenic potential	Test effects on genetic stability and mutations in bacteria (Ames test) or mammalian cells in culture; dominant lethal test and clastogenicity in mice.

Confounding Factors in Clinical Trials

A. The Variable Natural History of Most Diseases

Many diseases tend to wax and wane in severity; some disappear spontaneously, even, on occasion, cancer. A good experimental design takes into account the natural history of the disease by evaluating a large enough population of subjects over a sufficient period of time. Further protection against errors of interpretation caused by disease fluctuations is sometimes provided by using a **crossover design,** which consists of alternating periods of administration of test drug, placebo preparation (the control), and the standard treatment (positive control), if any, in each subject. These sequences are systematically varied, so that different subsets of patients receive each of the possible sequences of treatment.

B. The Presence of Other Diseases and Risk Factors

Known and unknown diseases and risk factors (including lifestyles of subjects) may influence the results of a clinical study. For example, some diseases alter the pharmacokinetics of drugs (see Chapters 3 through 5). Other drugs and some foods alter the pharmacokinetics of many drugs. Concentrations of blood or tissue components being monitored as a measure of the effect of the new agent may be influenced by other diseases or other drugs. Attempts to avoid this hazard usually involve the crossover technique (when feasible) and proper selection and assignment of patients to each of the study groups. This requires obtaining accurate diagnostic tests, medical and pharmacologic histories (including use of recreational drugs), and the use of statistically valid methods of randomization in assigning subjects to particular study groups. There is growing interest in analyzing genetic variations as part of the trial that may influence whether a person responds to a particular drug. It has been shown that age, gender, and pregnancy influence the pharmacokinetics of some drugs, but these factors have not been adequately studied because of legal restrictions and reluctance to expose these populations to unknown risks.

C. Subject and Observer Bias and Other Factors

Most patients tend to respond in a positive way to any therapeutic intervention by interested, caring, and enthusiastic medical personnel. The manifestation of this phenomenon in the subject is the **placebo response** (Latin, "I shall please") and may involve objective physiologic and biochemical changes as well as changes in subjective complaints associated with the disease. The placebo response is usually quantitated by administration of an inert material with exactly the same physical appearance, odor, consistency, etc, as the active dosage form. The magnitude of the response varies considerably from patient to patient and may also be influenced by the duration of the study. In some conditions, a positive response may be noted in as many as 30–40% of subjects given placebo. Placebo adverse effects and "toxicity" also occur but usually involve subjective effects: stomach upset, insomnia, sedation, and so on.

Subject bias effects can be quantitated—and minimized relative to the response measured during active therapy—by the **single-blind** design. This involves use of a placebo as described above, administered to the same subjects in a crossover design, if possible, or to a separate control group of well-matched subjects. Observer bias can be taken into account by disguising the identity of the medication being used—placebo or active form—from both the subjects and the personnel evaluating the subjects' responses (**double-blind** design). In this design, a third party holds the code identifying each medication packet, and the code is not broken until all the clinical data have been collected.

Drug effects seen in clinical trials are obviously affected by the patient taking the drugs at the dose and frequency prescribed. In a recent phase 2 study, one third of the patients who said they were taking the drug were found by blood analysis to have not taken the drug. Confirmation of **compliance** with protocols (also known as **adherence**) is a necessary element to consider.

Drug Studies—The Types of Evidence*

As described in this chapter, drugs are studied in a variety of ways, from 30-minute test tube experiments with isolated enzymes and receptors to decades-long observations of populations of patients. The conclusions that can be drawn from such different types of studies can be summarized as follows.

Basic research is designed to answer specific, usually single, questions under tightly controlled laboratory conditions, eg, does drug *x* inhibit enzyme *y*? The basic question may then be extended, eg, if drug *x* inhibits enzyme *y*, what is the concentration-response relationship? Such experiments are usually reproducible and often lead to reliable insights into the mechanism of the drug's action.

First-in-human studies include phase 1–3 trials. Once a drug receives FDA approval for use in humans, *case reports* and *case series* consist of observations by clinicians of the effects of drug (or other) treatments in one or more patients. These results often reveal unpredictable benefits and toxicities but do not generally test a prespecified hypothesis and cannot prove cause and effect. *Analytic epidemiologic studies* consist of observations designed to test a specified hypothesis, eg, that thiazolidinedione antidiabetic drugs are associated with adverse cardiovascular events. *Cohort* epidemiologic studies utilize populations of patients that have (exposed group) and have not (control group) been exposed to the agents under study and ask whether the exposed groups show a higher or lower incidence of the effect. *Case control* epidemiologic studies utilize populations of patients that have displayed the end point under study and ask whether they have been exposed or not exposed to the drugs in question. Such epidemiologic studies add weight to conjectures but cannot control all confounding variables and therefore cannot conclusively prove cause and effect.

Meta-analyses utilize rigorous evaluation and grouping of similar studies to increase the number of subjects studied and hence the statistical power of results obtained in multiple published studies. While the numbers may be dramatically increased by meta-analysis, the individual studies still suffer from their varying methods and end points, and a meta-analysis cannot prove cause and effect.

Large randomized controlled trials (**RCT**s) are designed to answer specific questions about the effects of medications on clinical end points or important surrogate end points, using large enough samples of patients and allocating them to control and experimental treatments using rigorous randomization methods. Randomization is the best method for distributing all foreseen confounding factors, as well as unknown confounders, equally between the experimental and control groups. When properly carried out, such studies are rarely invalidated and are considered the gold standard in evaluating drugs.

A critical factor in evaluating the data regarding a new drug is *access to all the data.* Unfortunately, many large studies are never published because the results are negative, ie, the new drug is *not* better than the standard therapy. This missing data phenomenon falsely exaggerates the benefits of new drugs because negative results are hidden.

[*]I thank Ralph Gonzales, MD, for helpful comments.

The various types of studies and the conclusions that may be drawn from them are described in the accompanying text box. (See Box: Drug Studies—The Types of Evidence.)

The Food & Drug Administration

The FDA is the administrative body that oversees the drug evaluation process in the USA and grants approval for marketing of new drug products. To receive FDA approval for marketing, the originating institution or company (almost always the latter) must submit evidence of safety and effectiveness. Outside the USA, the regulatory and drug approval process is generally similar to that in the USA.

As its name suggests, the FDA is also responsible for certain aspects of food safety, a role it shares with the US Department of Agriculture (USDA). Shared responsibility results in complications when questions arise regarding the use of drugs, eg, antibiotics, in food animals. A different type of problem arises when so-called food supplements are found to contain active drugs, eg, sildenafil analogs in "energy food" supplements.

The FDA's authority to regulate drugs derives from specific legislation (Table 1–5). If a drug has not been shown through adequately controlled testing to be "safe and effective" for a specific use, it cannot be marketed in interstate commerce for this use.[*]

Unfortunately, "safe" can mean different things to the patient, the physician, and society. Complete absence of risk is impossible to demonstrate, but this fact may not be understood by members of the public, who frequently assume that any medication sold with the approval of the FDA should be free of serious "side effects." This confusion is a major factor in litigation and dissatisfaction with aspects of drugs and medical care.

The history of drug regulation in the USA (Table 1–5) reflects several health events that precipitated major shifts in public opinion. For example, the Federal Food, Drug, and Cosmetic Act of 1938 was largely a reaction to deaths associated with the use of a preparation of sulfanilamide marketed before it and its vehicle were adequately tested. Similarly, the Kefauver-Harris Amendments of 1962 were, in part, the result of a teratogenic drug disaster involving thalidomide. This agent was introduced in Europe in 1957–1958 and was marketed as a "nontoxic" hypnotic and promoted as being especially useful during pregnancy. In 1961, reports were published suggesting that thalidomide was responsible for a dramatic increase in the incidence of a rare birth defect called phocomelia, a condition involving shortening or complete absence of the arms and legs. Epidemiologic studies provided strong evidence for the association of this defect with thalidomide use by women during the first trimester of pregnancy, and the drug was withdrawn from sale worldwide. An estimated 10,000 children were born with birth defects because of maternal exposure to this one agent. The tragedy led to the requirement for more extensive testing of new drugs for teratogenic effects and stimulated passage of the Kefauver-Harris Amendments of 1962, even though the drug was not then approved for use in the USA. In spite of its disastrous fetal toxicity and effects in pregnancy, thalidomide is a relatively safe drug for humans other than the fetus. Even the most serious risk of toxicities may be avoided or managed if understood, and despite its toxicity, thalidomide is now approved by the FDA for limited use as a potent immunoregulatory agent and to treat certain forms of leprosy.

Clinical Trials: The IND & NDA

Once a new drug is judged ready to be studied in humans, a Notice of Claimed Investigational Exemption for a New Drug (IND) must be filed with the FDA (Figure 1–6). The IND includes (1) information on the composition and source of the drug, (2) chemical and manufacturing information, (3) all data from animal studies, (4) proposed plans for clinical trials, (5) the names and credentials of physicians who will conduct the clinical trials, and (6) a compilation of the key preclinical data relevant to study of the drug in humans that have been made available to investigators and their institutional review boards.

[*]Although the FDA does not directly control drug commerce within states, a variety of state and federal laws control interstate production and marketing of drugs.

TABLE 1–5 Some major legislation pertaining to drugs in the USA.

Law	Purpose and Effect
Pure Food and Drug Act of 1906	Prohibited mislabeling and adulteration of drugs.
Opium Exclusion Act of 1909	Prohibited importation of opium.
Amendment (1912) to the Pure Food and Drug Act	Prohibited false or fraudulent advertising claims.
Harrison Narcotic Act of 1914	Established regulations for use of opium, opiates, and cocaine (marijuana added in 1937).
Food, Drug, and Cosmetic Act of 1938	Required that new drugs be safe as well as pure (but did not require proof of efficacy). Enforcement by FDA.
Durham-Humphrey Act of 1952	Vested in the FDA the power to determine which products could be sold without prescription.
Kefauver-Harris Amendments (1962) to the Food, Drug, and Cosmetic Act	Required proof of efficacy as well as safety for new drugs and for drugs released since 1938; established guidelines for reporting of information about adverse reactions, clinical testing, and advertising of new drugs.
Comprehensive Drug Abuse Prevention and Control Act (1970)	Outlined strict controls in the manufacture, distribution, and prescribing of habit-forming drugs; established drug schedules and programs to prevent and treat drug addiction.
Orphan Drug Amendment of 1983	Provided incentives for development of drugs that treat diseases with fewer than 200,000 patients in USA.
Drug Price Competition and Patent Restoration Act of 1984	Abbreviated new drug applications for generic drugs. Required bioequivalence data. Patent life extended by amount of time drug delayed by FDA review process. Cannot exceed 5 extra years or extend to more than 14 years post-NDA approval.
Prescription Drug User Fee Act (1992, reauthorized 2007, 2012)	Manufacturers pay user fees for certain new drug applications. "Breakthrough" products may receive special category approval after expanded phase 1 trials (2012).
Dietary Supplement Health and Education Act (1994)	Established standards with respect to dietary supplements but prohibited full FDA review of supplements and botanicals as drugs. Required the establishment of specific ingredient and nutrition information labeling that defines dietary supplements and classifies them as part of the food supply but allows unregulated advertising.
Bioterrorism Act of 2002	Enhanced controls on dangerous biologic agents and toxins. Seeks to protect safety of food, water, and drug supply.
Food and Drug Administration Amendments Act of 2007	Granted FDA greater authority over drug marketing, labeling, and direct-to-consumer advertising; required post-approval studies, established active surveillance systems, made clinical trial operations and results more visible to the public.
Biologics Price Competition and Innovation Act of 2009	Authorized the FDA to establish a program of abbreviated pathways for approval of "biosimilar" biologics (generic versions of monoclonal antibodies, etc).
FDA Safety and Innovation Act of 2012	Renewed FDA authorization for accelerated approval of urgently needed drugs; established new accelerated process, "breakthrough therapy," in addition to "priority review," "accelerated approval," and "fast-track" procedures.

It often requires 4–6 years of clinical testing to accumulate and analyze all required data. Testing in humans is begun only after sufficient acute and subacute animal toxicity studies have been completed. Chronic safety testing in animals, including carcinogenicity studies, is usually done concurrently with clinical trials. In each phase of the clinical trials, volunteers or patients must be informed of the investigational status of the drug as well as the possible risks and must be allowed to decline or to consent to participate and receive the drug. In addition to the approval of the sponsoring organization and the FDA, an interdisciplinary institutional review board (IRB) at each facility where the clinical drug trial will be conducted must review and approve the scientific and ethical plans for testing in humans.

In **phase 1**, the effects of the drug as a function of dosage are established in a small number (20–100) of healthy volunteers. If the drug is expected to have significant toxicity, as may be the case in cancer and AIDS therapy, volunteer patients with the disease participate in phase 1 rather than normal volunteers. Phase 1 trials are done to determine the probable limits of the safe clinical dosage range. These trials may be nonblind or "open"; that is, both the investigators and the subjects know what is being given. Alternatively, they may be "blinded" and placebo controlled. Many predictable toxicities are detected in this phase. Pharmacokinetic measurements of absorption, half-life, and metabolism are often done. Phase 1 studies are usually performed in research centers by specially trained clinical pharmacologists.

In **phase 2**, the drug is studied in patients with the target disease to determine its efficacy ("proof of concept"), and the doses to be used in any follow-on trials. A modest number of patients (100–200) are studied in detail. A single-blind design may be used, with an inert placebo medication and an established active drug (positive control) in addition to the investigational agent. Phase 2 trials are usually done in special clinical centers (eg, university hospitals). A broader range of toxicities may be detected in this phase. Phase 2 trials have the highest rate of drug failures, and only 25% of innovative drugs move on to phase 3.

In **phase 3**, the drug is evaluated in much larger numbers of patients with the target disease—usually thousands—to further establish and confirm safety and efficacy. Using information gathered in phases 1 and 2, phase 3 trials are designed to minimize errors caused by placebo effects, variable course of the disease, etc. Therefore, double-blind and crossover techniques are often used. Phase 3 trials are usually performed in settings similar to those anticipated for the ultimate use of the drug. Phase 3 studies can be difficult to design and execute and are usually expensive because of the large numbers of patients involved and the masses of data that must be collected and analyzed. The drug is formulated as intended for the market. The investigators are usually specialists in the disease being treated. Certain toxic effects, especially those caused by immunologic processes, may first become apparent in phase 3.

If phase 3 results meet expectations, application is made for permission to market the new agent. Marketing approval requires submission of a New Drug Application (NDA)—or for biologicals, a Biological License Application (BLA)—to the FDA. The application contains, often in hundreds of volumes, full reports of all preclinical and clinical data pertaining to the drug under review. The number of subjects studied in support of the new drug application has been increasing and currently averages more than 5000 patients for new drugs of novel structure (new molecular entities). The duration of the FDA review leading to approval (or denial) of the new drug application may vary from months to years. If problems arise, eg, unexpected but possibly serious toxicities, additional studies may be required and the approval process may extend to several additional years.

In cases of urgent need (eg, cancer chemotherapy), the process of preclinical and clinical testing and FDA review may be accelerated. For serious diseases, the FDA may permit extensive but controlled marketing of a new drug before phase 3 studies are completed; for life-threatening diseases, it may permit controlled marketing even before phase 2 studies have been completed. "Fast track," "priority approval," and "accelerated approval" are FDA programs that have been in place to speed entry of new drugs into the marketplace. In 2012, an additional special category of "breakthrough" products (eg, for cystic fibrosis) was approved for restricted marketing after expanded phase 1 trials (Table 1–5). Roughly 50% of drugs in phase 3 trials involve early, controlled marketing. Such accelerated approval is usually granted with the requirement that careful monitoring of the effectiveness and toxicity of the drug be carried out and reported to the FDA. Unfortunately, FDA enforcement of this requirement has not always been adequate.

Once approval to market a drug has been obtained, **phase 4** begins. This constitutes monitoring the safety of the new drug under actual conditions of use in large numbers of patients. The importance of careful and complete reporting of toxicity by physicians after marketing begins can be appreciated by noting that many important drug-induced effects have an incidence of 1 in 10,000 or less and that some adverse effects may become apparent only after chronic dosing. The sample size required to disclose drug-induced events or toxicities is very large for such rare events. For example, several hundred thousand patients may have to be exposed before the first case is observed of a toxicity that occurs with an average incidence of 1 in 10,000. Therefore, low-incidence drug effects are not generally detected before phase 4 no matter how carefully the studies are executed. Phase 4 has no fixed duration. As with monitoring of drugs granted accelerated approval, phase 4 monitoring has often been lax.

The time from the filing of a patent application to approval for marketing of a new drug may be 5 years or considerably longer. Since the lifetime of a patent is 20 years in the USA, the owner of the patent (usually a pharmaceutical company) has exclusive rights for marketing the product for only a limited time after approval of the new drug application. Because the FDA review process can be lengthy (300–500 days for evaluation of an NDA), the time consumed by the review is sometimes added to the patent life. However, the extension (up to 5 years) cannot increase the total life of the patent to more than 14 years after approval of a new drug application. The Patient Protection and Affordable Care Act of 2010 provides for 12 years of patent protection for new drugs. After expiration of the patent, any company may produce the drug, file an abbreviated new drug application (ANDA), demonstrate required equivalence, and, with FDA approval, market the drug as a **generic** product without paying license fees to the original patent owner. Currently, more than half of prescriptions in the USA are for generic drugs. Even biotechnology-based drugs such as antibodies and other proteins are now qualifying for generic designation, and this has fueled regulatory concerns. More information on drug patents is available at the FDA website at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/ucm079031.htm.

A **trademark** is the drug's proprietary trade name and is usually registered; this registered name may be legally protected as long as it is used. A generically equivalent product, unless specially licensed, cannot be sold under the trademark name and is often designated by the official generic name. Generic prescribing is described in Chapter 65.

Conflicts of Interest

Several factors in the development and marketing of drugs result in conflicts of interest. Use of pharmaceutical industry funding to support FDA approval processes raises the possibility of conflicts of interest within the FDA. Supporters of this policy point out that chronic FDA underfunding by the government allows for few alternatives. Another important source of conflicts of interest is the dependence of the FDA on outside panels of experts who are recruited from the scientific and clinical community to advise the government agency on questions regarding drug approval or withdrawal. Such experts are often recipients of grants from the companies producing the drugs in question. The need for favorable data in the new drug application leads to phase 2 and 3 trials in which the new agent is compared only to placebo, not to older, effective drugs. As a result, data regarding the efficacy and toxicity of the new drug *relative to a known effective agent* may not be available when the new drug is first marketed.

Manufacturers promoting a new agent may pay physicians to use it in preference to older drugs with which they are more familiar. Manufacturers sponsor small and often poorly designed clinical studies after marketing approval and aid in the publication of favorable results but may retard publication of unfavorable results. The need for physicians to meet continuing medical education (CME) requirements in order to maintain their licenses encourages manufacturers to sponsor conferences and courses, often in highly attractive vacation sites, and new drugs are often featured in such courses. Finally, the common practice of distributing free samples of new drugs to practicing physicians has both positive and negative effects. The samples allow physicians to try out new drugs without incurring any cost to the patient. On the other hand, new drugs are usually much more expensive than older agents and when the free samples run out, the patient (or insurance carrier) may be forced to pay much more for treatment than if the older, cheaper, and possibly equally effective drug were used. Finally, when the patent for a drug is nearing expiration, the patent-holding manufacturer may try to extend its exclusive marketing privilege by paying generic manufacturers to *not* introduce a generic version ("pay to delay").

Adverse Drug Reactions

An adverse drug event (ADE) or reaction to a drug (ADR) is a harmful or unintended response. Adverse drug reactions are claimed to be the fourth leading cause of death, higher than pulmonary disease, AIDS, accidents, and automobile deaths. The FDA has further estimated that 300,000 preventable adverse events occur in hospitals, many as a result of confusing medical information or lack of information (eg, regarding drug incompatibilities). Some adverse reactions, such as overdose, excessive effects, and drug interactions, may occur in anyone. Adverse reactions occurring only in susceptible patients include intolerance, idiosyncrasy (frequently genetic in origin), and allergy (usually immunologically mediated). During IND studies and clinical trials before FDA approval, all adverse events (serious, life-threatening, disabling, reasonably drug related, or unexpected) must be reported. After FDA approval to market a drug, surveillance, evaluation, and reporting must continue for any adverse events that are related to use of the drug, including overdose, accident, failure of expected action, events occurring from drug withdrawal, and unexpected events not listed in labeling. Events that are both serious and unexpected must be reported to the FDA within 15 days. The ability to predict and avoid adverse drug reactions and optimize a drug's therapeutic index is an increasing focus of pharmacogenetic and personalized medicine. It is hoped that greater use of electronic health records will reduce some of these risks (see Chapter 65).

Orphan Drugs & Treatment of Rare Diseases

Drugs for rare diseases—so-called orphan drugs—can be difficult to research, develop, and market. Proof of drug safety and efficacy in small populations must be established, but doing so is a complex process. Furthermore, because basic research in the pathophysiology and mechanisms of rare diseases receives relatively little attention or funding in both academic and industrial settings, recognized rational targets for drug action may be few. In addition, the cost of developing a drug can greatly influence priorities when the target population is relatively small. Funding for development of drugs for rare diseases or ignored diseases that do not receive priority attention from the traditional industry has received increasing support via philanthropy or similar funding from not-for-profit foundations such as the Cystic Fibrosis Foundation, the Huntington's Disease Society of America, and the Gates Foundation.

The Orphan Drug Amendment of 1983 provides incentives for the development of drugs for treatment of a rare disease or condition defined as "any disease or condition which (a) affects less than 200,000 persons in the USA or (b) affects more than 200,000 persons in the USA but for which there is no reasonable expectation that the cost of developing and making available in the USA a drug for such disease or condition will be recovered from sales in the USA of such drug." Since 1983, the FDA has approved for marketing more than 300 orphan drugs to treat more than 82 rare diseases.

SOURCES OF INFORMATION

Students who wish to review the field of pharmacology in preparation for an examination are referred to *Pharmacology: Examination and Board Review,* by Trevor, Katzung, Kruidering-Hall, and Masters (McGraw-Hill, 2013). This book provides approximately 1000 questions and explanations in USMLE format. A short study guide is *USMLE Road Map: Pharmacology,* by Katzung and Trevor (McGraw-Hill, 2006). *Road Map* contains numerous tables, figures, mnemonics, and USMLE-type clinical vignettes.

The references at the end of each chapter in this book were selected to provide reviews or classic publications of information specific to those chapters. More detailed questions relating to basic or clinical research are best answered by referring to the journals covering general pharmacology and clinical specialties. For the student and the physician, three periodicals can be recommended as especially useful sources of current information about drugs: *The New England Journal of Medicine*, which publishes much original drug-related clinical research as well as frequent reviews of topics in pharmacology; *The Medical Letter on Drugs and Therapeutics*, which publishes brief critical reviews of new and old therapies and *Prescriber's Letter*, a monthly comparison of new and older drug therapies with much useful advice. On the Internet/World Wide Web, two sources can be particularly recommended: the Cochrane Collaboration and the FDA site (see reference list below).

Other sources of information pertinent to the United States should be mentioned as well. The "package insert" is a summary of information that the manufacturer is required to place in the prescription sales package; *Physicians' Desk Reference (PDR)* is a compendium of package inserts published annually with supplements twice a year. It is sold in bookstores and distributed free to licensed physicians. The package insert consists of a brief description of the pharmacology of the product. This brochure contains

much practical information, and it is also used as a means of shifting liability for untoward drug reactions from the manufacturer onto the practitioner. Therefore, the manufacturer typically lists every toxic effect ever reported, no matter how rare. *Micromedex* is an extensive subscription website maintained by Truven Corporation (www.micromedexsolutions.com). It provides downloads for personal digital assistant devices, online drug dosage and interaction information, and toxicologic information. A useful and objective quarterly handbook that presents information on drug toxicity and interactions is *Drug Interactions: Analysis and Management*. Finally, the FDA maintains an Internet website that carries news regarding recent drug approvals, withdrawals, warnings, etc. It can be accessed at http://www.fda.gov. The MedWatch drug safety program is a free e-mail notification service that provides news of FDA drug warnings and withdrawals. Subscriptions may be obtained at https://service.govdelivery.com/service/user.html?code=USFDA.

REFERENCES

Avorn J: Debate about funding comparative effectiveness research. N Engl J Med 2009;360:1927.

Avorn J: *Powerful Medicines: The Benefits and Risks and Costs of Prescription Drugs.* Alfred A. Knopf, 2004.

Bauchner H, Fontanarosa PB: Restoring confidence in the pharmaceutical industry. JAMA 2013;309:607.

Boutron I et al: Reporting and interpretation of randomized controlled trials with statistically nonsignificant results for primary outcomes. JAMA 2010;303:2058.

Brown WA: The placebo effect. Sci Am 1998;1:91.

Cochrane Collaboration website: www.thecochranelibrary.com.

DiMasi JA: Rising research and development costs for new drugs in a cost containment environment. J Health Econ 2003;22:151.

Downing NS et al: Regulatory review of novel therapeutics—Comparison of three regulatory agencies. N Engl J Med 2012;366:2284.

Drug Interactions: Analysis and Management (quarterly). Wolters Kluwer Publications.

Emanuel EJ, Menikoff J: Reforming the regulations governing research with human subjects. N Engl J Med 2011;365:1145.

Evans RP: *Drug and Biological Development: From Molecule to Product and Beyond.* Springer, 2007.

FDA accelerated approval website: http://www.fda.gov/ForConsumers/ByAudience/ForPatientAdvocates/SpeedingAccesstoImportantNewTherapies/ucm128291.htm.

FDA website: http://www.fda.gov.

Goldacre B: *Bad Pharma*. Faber & Faber, 2012.

Hennekens CMH, DeMets D: Statistical association and causation. Contributions of different types of evidence. JAMA 2011;305:1134.

Huang S-M, Temple R: Is this the drug or dose for you? Impact and consideration of ethnic factors in global drug development, regulatory review, and clinical practice. Clin Pharmacol Ther 2008;84:287; or http://www.fda.gov/cder/genomics/publications.htm.

Kesselheim AS et al: Whistle-blowers experiences in fraud litigation against pharmaceutical companies. N Engl J Med 2010;362:1832.

Koslowski S et al: Developing the nation's biosimilar program. N Engl J Med 2011;365:385.

Landry Y, Gies J-P: Drugs and their molecular targets: An updated overview. Fund & Clin Pharmacol 2008;22:1.

Lee C-J et al: *Clinical Trials of Drugs and Biopharmaceuticals*. CRC Publishing, 2005.

The Medical Letter on Drugs and Therapeutics. The Medical Letter, Inc.

Ng R: *Drugs from Discovery to Approval*. Wiley-Blackwell, 2008.

Pharmaceutical Research and Manufacturers of America website: http://www.phrma.org.

Pharmacology: Examination & Board Review, 10th ed. 2013 McGraw-Hill Companies, Inc.

Prescriber's Letter. Stockton, California; prescribersletter.com.

Rockey SJ, Collins FS: Managing financial conflict of interest in biomedical research. JAMA 2010;303:2400.

Scheindlin S: Demystifying the new drug application. Mol Interventions 2004;4:188.

Sistare FD, DeGeorge JJ: Preclinical predictors of clinical safety: Opportunities for improvement. Clin Pharmacol Ther 2007;82(2):210.

Stevens AJ et al: The role of public sector research in the discovery of drugs and vaccines. N Engl J Med 2011;364:535.

Top 200 Drugs of 2011: http://www.pharmacytimes.com/publications/issue/2012/July2012/Top-200-Drugs-of-2011.

USMLE Road Map: Pharmacology. McGraw-Hill Companies, Inc. 2006.

Zarin DA et al: Characteristics of clinical trials registered in ClinicalTrials.gov, 2007-2010. JAMA 2012;307:1838.

CASE STUDY ANSWER

In the case study, the patient intravenously self-administered an overdose of methamphetamine, a weak base. This drug is freely filtered at the glomerulus, but can be rapidly reabsorbed in the renal tubule. Administration of ammonium chloride acidifies the urine, converting a larger fraction of the drug to the protonated, charged form, which is poorly reabsorbed and thus more rapidly eliminated. Note that not all experts recommend forced diuresis and urinary pH manipulation after methamphetamine overdose because of the risk of renal damage (see Figure 1–5).